

**IV. REMARKS****A. Status of the Claims**

Claims 24 and 28-46 are pending. Claims 1-23 and 44-91 have been withdrawn in response to the restriction requirement and claims 25-27 have been canceled. Claims 44-46 have been added as new. Support for amended claim 24 can be found, *inter alia*, on page 6, line 14 through page 8, line 5. Support for amended claim 32 can be found in the specification on page 6, lines 19-24. Support for new claim 44 can be found in the specification on page 34, lines 1-4. Support for new claims 45 and 46 can be found, *inter alia*, on page 6, line 14 through page 8, line 5 and page 34, lines 1-4. Claims 24, 28, 29, 32, 33, 36, 37 and 43 have been amended.

**B. Restriction Requirement**

In the Restriction and Election of Species requirement, the Examiner required restriction to one of the following inventions:

- Group I: Claims 1-23 and 75-78 drawn to a method of defining (identifying) a portion or fragment of a compound classified in class 435, subclass 7.1;
- Group II: Claims 24-43 drawn to a method of identifying compounds which have binding affinity for a target receptor, classified in class 435, subclass 7.1;
- Group III: Claims 44-48 and 63-74 drawn to a method of identifying a portion of PDE IV inhibitors, classified in class 435, subclass 7.4;
- Group IV: Claims 49-53 drawn to a method of identifying compounds which inhibit PDE IV by screening, classified in class 435, subclass 4+; or
- Group V: Claims 54-62 drawn to a method of designing a three-dimensional structure, classified in class 435, subclass 7.1.

In response to the restriction requirement, Applicants hereby elect Group II, claims 24-43, drawn to a method of screening, classified in class 435, subclass 7.1, without traverse, for examination.

**C. Election of Species Requirement**

The Examiner also required election of species to a single disclosed species for each of the subgroups. The subgroups within Group II are as follows:

**Subgroup A: Functional groups:**

1. Carboxyl
2. Hydroxyl
3. Keto
4. Amino
5. Nitro
6. Sulfhydryl

**Subgroup B: Source of Compound:**

1. Combinatorial library:
  - Peptide
  - Ethers
  - Phosphonates
2. Natural product extracts
3. Microbial or other cell culture broths
4. Synthetic products
5. Synthetic analogs
6. Intermediates

**Subgroup C: Chemical groups:**

1. Organic
2. Inorganic
3. Biological molecules

In response to the election of species requirement, Applicants elect species 4 in subgroup A, directed to amino functional groups, species 4 in subgroup B, directed to synthetic products, and species 1 in subgroup C, directed to organic chemical groups.

**D. Discussion of Examiner's Rejections From the Parent Case**

Applicants respectfully submit the following arguments in view of rejections previously made by the Examiner under 35 U.S.C. § 112, first and second paragraphs during the prosecution of the parent case (U.S. Patent Application No. 09/191,780).

**I. 35 U.S.C. § 112, First Paragraph**

With regard to the grammatical errors and the status of the co-pending applications, the specification has been amended to correct the errors and to include the status of the co-pending applications mentioned therein.

**II. 35 U.S.C. § 112, Second Paragraph**

With regard to the rejection in the Office Action dated July 26, 2000 from the parent case based on lack of antecedent basis for the term "one or more compounds of interest" in claims 24 and 33, the preamble of claim 24 has been amended to recite "one or more compounds of interest."

In the Office Action dated July 26, 2000 from the parent case, the Examiner stated that step (a) of claim 24 is "indefinite as to the means by which the key components of a fragments [sic] of one or more chemical compounds is [sic, are] identified", and that the metes and bounds of the claimed "key component" and "one or more fragments of the chemical compounds" are indefinite." In the final Office Action dated March 27, 2001 the Examiner further stated that "it is not the terminology that is at issue. Rather the steps or means by which the one or more key component fragments are identified... there is no evidence to show the means of inspecting (?) [sic] The chemical structure." The Examiner suggested that Applicants point out the portion of the specification where inspection is performed to identify portions of a chemical structure which may be involved in binding to a target receptor.

Applicants respectfully direct the Examiner's attention to the text in the specification at page 11, lines 19-21, where the term "key component fragment" is defined. The specification states:

For purposes of the present invention, the phrase "key component fragment" means a portion of a molecule which potentially contributes to the binding affinity of that molecule for a target receptor.

Further, it is a fundamental axiom of patent law that Applicants may act as their own lexicographer and define terminology used in the specification. Here, the phrase "key component fragment" is clearly defined as "a portion of a molecule which potentially contributes to the binding affinity of that molecule for a target receptor." The specification states on page 16, lines 9-10, that "one or more key component fragments are selected which may impart affinity for the target receptor."

Moreover, the concept of determining the binding affinity of a molecule for a receptor is readily understood by one skilled in the art. For example, a skilled artisan can quantitatively measure the affinity of an antibody for antigen by the method of equilibrium dialysis. From measurements of the equilibrium concentrations of free and bound antigen, starting with different initial concentrations of antigen, one can apply a simple formula (the "Scatchard Equation") in order to determine the equilibrium association constant (dissociation constant) and valence of an antibody (See: Richard A. Goldsby, *et al.*, Kuby, Immunology, 3<sup>rd</sup> Ed., Ch. 6 (1997)).

The specification further explains at page 16, lines 13-16 that "[a]dditional compounds containing some or all of the key component fragments are then identified as analogs. The analogs can be identified through review of existing literature to identify structurally similar compounds." Analogs are defined on page 11, lines 9-10, as "a chemical compound possessing a similar structure to a model compound of interest, e.g., compound from synthetic products."

Applicants also direct the Examiner's attention to the discussion of one preferred embodiment of the invention related to screening for compounds that inhibit PDE IV receptors on page 42, lines 19-29 through page 47, line 14. In this embodiment, a compound known to be a PDE IV inhibitor, shown in Figure 1, was chosen as a prototype PDE IV inhibitor, and two analogs of the prototype compound, also shown in Figure 1, were chosen as haptens for generating antibodies with reactivity against those particular chemical structures. The structures presented in Figure 1 clearly elucidate the structural inspection and comparison performed in identifying these compounds. Other examples of analogs were also given, which were identified by a review of the literature in the field of PDE IV inhibitors. See pages 43-44 for discussion of these additional analogs (rolipram, Ariflo, Piclamilast and CDP 840).

Solely for purposes of expediting the prosecution, Applicants have amended claim 24 step (b) so that it now recites the definition of "key component fragment" provided in the specification.

In the July 26, 2000 Office Action, the Examiner also rejected claim 24 step b) as being indefinite for not making clear as to what or how the key component fragments are exposed. In response, Applicants direct the Examiner's attention to the specification, page 17, lines 7-13, which recites:

When the analogs are coupled to a carrier molecule, such as KLH, an "analog-carrier conjugate" is created. This process, known as haptenization, results the generation or production of monoclonal antibodies with specificity for the compound. The free end of the molecule which is exposed to the solution (the "solvent exposed portion") is most likely to be recognized as a hapten immune system. Therefore antibodies will be generated which exhibit selectivity for the solvent exposed portion of the molecule. The sterically hindered portion of the analog does not elicit a specific antibody reaction because it is not accessible to the antibodies.

In response to the Examiner's rejection in the July 26, 2000 Office Action that the term "analog" in claim 26 and 32 is confusing, claims 26 and 32 have been amended for clarity and to expedite prosecution. Applicants explain that the amendments are not a narrowing amendments because the meaning and scope of the claims have not been changed. Applicants also direct the

Examiner's attention to the Definition section of the Specification on page 10, where the term "analog-carrier conjugate" is defined.

With regard to the Examiner's rejection in the July 26, 2000 Office Action that the phrase "analog-carrier conjugates defining a portion of the entire surface conformation of the one or more chemical compounds" is indefinite, the Examiner is respectfully directed to page 10 of the Specification wherein the term "surface conformation" is defined to mean "a three-dimensional contour of a molecule, portion of a molecule, or group of molecules." Thus the term "surface conformation" is clearly defined in the Specification. Applicants also point out that even without this definition the phrase "surface confirmation" would readily be understood by one of ordinary skill in the art.

Applicants point out that the Examiner in the July 26, 2000 also rejected claim 32 as confusing "in that the claims [sic] recite for construction of one or more analog-carrier conjugates which is inconsistent with the base claim which does not recite for a construction... [and that] the phrase 'functional groups' lack [sic] antecedent support from the base claim." Applicants believe that claim 32 as currently amended overcomes the Examiner's rejection.

### **III     35 U.S.C. § § 102 and 103**

During the prosecution of parent application no. 09/191,780, the Examiner made the following rejections in his Final Office mailed March 27, 2001:

Claims 24-40 and 43 under 35 U.S.C. § 102(b) were rejected as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as obvious over Cucumel, et al. (Journal of Neuroimmunology)(“the Cucumel reference”). The Examiner specifically asserted that the Cucumel reference discloses “a method of identifying a compound which has binding affinity for a target receptor comprising identifying the antiidiotypic antibodies opiate epitope binding region and making analogs of these epitope binding region, conjugating to an immunogenic form to

KLH as carrier and administering into an animal to generate a pool of antibodies. The Examiner further asserted that the Cucumel reference does involve the use of monoclonal antibodies and that it therefore positively teaches the argued monoclonal antibody.

Claims 24-27, 30-34, 36-40 and 43 were rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as obvious over Farid, et al. (Can. Biochem. Cell Biol.) ("the Farid reference") or WO 91/17179 to Jameson ("the Jameson reference"). The Examiner asserted that the Farid reference "describes the specific method steps of the claimed method reciting broad claimed components." The Examiner also asserted that the Jameson reference discloses the argued mab.

Claims 24-34, 36-40 and 43 were rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as obvious over Chamat, et al. (J. Immunology) ("the Chamat reference"). The Examiner argued that the body of claim 24 "recites only assaying the immobilized antibodies to screen one or more compounds", and that this is taught by the Chamat reference at page 3805, col. 2, 3<sup>rd</sup> paragraph.

Claims 24-27, 29-34, 36-40 and 43 were rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative under 35 U.S.C. § 103(a) as obvious over Greene, et al. (U.S. Patent No. 5,637,677) ("the Greene reference"). The Examiner asserted that the same arguments as advanced in the rejection over the Chamat reference were applicable.

Applicants respectfully traverse these rejections. None of the cited references disclose or suggest each and every one of the method steps recited in amended claim 24 as set forth below.

Claim 24. (Currently amended) A method of identifying one or more compounds of interest which have binding affinity for a target receptor comprising:

(a) identifying one or more key component fragments of one or more chemical compounds having binding affinity for a target receptor wherein said key component fragment is a portion of a molecule which contributes to the binding affinity of that

molecule for the target receptor;

(b) coupling one or more analogs of the one or more chemical compounds to a carrier molecule to construct one or more analog-carrier conjugates, said analogs containing one or more of the key component fragments, said analogs being coupled to the carrier such that one or more of the key component fragments are exposed;

(c) utilizing the analog-carrier conjugates to generate monoclonal antibodies in vivo or in vitro that are able to define the exposed key component fragments; and

(d) measuring the dissociation constant for the binding of the monoclonal antibodies to the analogs to determine which monoclonal antibodies exhibit the strongest binding;

(e) immobilizing the monoclonal antibodies having the strongest binding on a support; and

(f) conducting a series of in-vitro assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest.

In response to the previous rejections in view of the various prior art references, Applicants first generally explain that step (f) of amended claim 24 recites that the immobilized monoclonal antibodies are used to conduct a series of *in-vitro* assays for screening one or more compounds of interest. None of the references cited by the Examiner teach or suggest the use of immobilized monoclonal antibodies for conducting *in-vitro* assays for screening compounds of interest. For at least this reason, none of the cited references anticipate or render obvious claim 24. As claims 27-32, 34-40 and 43 depend from and incorporate all of the limitations of claim 24 these claims also are not anticipated or rendered obvious in view of the cited references.

Applicants also point out that new independent claims 45 and 46 also have a step (f) which relates to immobilized monoclonal antibodies which are used to conduct a series of *in-vitro* assays for screening purpose. Therefore, these claims cannot be anticipated or rendered obvious by the cited references.

Further, new dependent claim 44 and new independent claim 46 are directed to *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products. None of the cited references teach or suggest the screening for synthetic compounds. Therefore, for this further reason, these new claims cannot be anticipated or

rendered obvious by the cited references.

Specifically, the Cucumel reference purportedly teaches that antibodies may be generated against synthetic peptides, such as the opioid agonist DSLET, and that these antibodies may be used to generate anti-idiotypic antibodies having the ability to bind to a opioid receptor. Even though the Cucumel reference discusses monoclonal anti-idiotypic antibodies, the monoclonal antibodies mentioned were described as being generated using a purified rabbit IgG fraction, i.e., an *in-vivo* process, wherein the anti-peptide antibodies themselves are used as immunogens (see page 185, col. 1, section no. 2.4.2). Thus, the anti-idiotypic antibodies discussed by the Cucumel reference are used to bind directly to the target receptor, and are not used to screen for compounds. Therefore, the Cucumel reference cannot teach or suggest step (f) of amended independent claim 24 and new claims 44-46 which recite, “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest”, (claims 24 and 45) or , “one or more compounds from synthetic products” (claims 44 or 46). Therefore, amended claim 24 and new claims 44-46 are neither anticipated nor obvious in view of the Cucumel reference. As claims 28-32, and 34-43 depend from claim 24, these claims are also not anticipated or obvious in view of the Cucumel reference.

Further, step (f) of new dependent claim 44 and independent claim 46 both recite, “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products” (emphasis added). Cucumel does not teach or suggest the screening for one or more compounds from synthetic products and therefore cannot anticipate or render obvious the present claims.

Thus, Cucumel does not either anticipate or make obvious the claims of the present invention.

The Examiner argued that the Farid reference “discloses a method of identifying a compound which has binding affinity for a target receptor comprising identifying the antiidiotypic antibodies TSH epitope binding region and making analogs of these epitope binding region, conjugating these to an immunogenic form to KLH as carrier and administering into an animal to generate a pool of antibodies”, i.e., *in-vivo* administration. Thus, as with Cucumel, the Farid reference is only directed to the use of antibodies *in vivo*. The Farid reference does not teach or suggest step (f) of the independent claim 24 or new claims 44-46 which recite, “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest”, (claims 24 and 45) or , “one or more compounds from synthetic products” (claims 44 or 46) (emphasis added). Therefore, amended claim 24 and new claims 44-46 are neither anticipated nor obvious in view of the Farid reference. As claims 28-32, 34-43 depend from claim 24, these claims are also not anticipated or obvious in view of the Farid reference.

Further, with regard to new claims 44 and 46 which recite “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products” (emphasis added), Farid does not teach or suggest the screening for one or more compounds from synthetic products and therefore cannot anticipate or render obvious the present claims.

The Examiner also rejected claims 24-27, 30-34, 36-40 and 43 in view of the Jameson reference. The Jameson reference also purports to identify the antiidiotypic antibodies viral epitope binding region and to make analogs of these epitope binding regions, conjugate them to an immunogenic form to KLH as carrier and administer them into an animal to generate a pool of antibodies, i.e., *in-vivo* administration. In particular, the Jameson reference purports to disclose antibodies which bind to CD4 protein and inhibit binding of the HIV-1 or HIV-2 to CD4, as well as antiidiotypic antibodies which are used for diagnostic purposes (for the detection of HIV-1 or HIV-2 in serum) or for therapeutic applications (as a vaccine). It describes the selection of

peptides and peptide analogs of the CDR3 of CD4, and the subsequent generation of antibodies (Ab1) against these sequences. The Jameson reference also purports to generate anti-idiotypic antibodies (Ab2) from the Ab1 when Ab1 were used to immunize animals.

However, the Jameson reference does not teach or suggest step (f) of amended independent claim 24 and new claims 44-46 which recite, “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest”, (claims 24 and 45) or , “one or more compounds from synthetic products” (claims 44 or 46). Therefore, amended claim 24 and new claims 44-46 are neither anticipated nor obvious in view of the Jameson reference. As claims 28-32, 34-43 depend from claim 24, these claims are also not anticipated or obvious in view of the Jameson reference.

Further, step (f) of new dependent claim 44 and new independent claim 46 both recite “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products” (emphasis added). Jameson does not teach or suggest the screening for one or more compounds from synthetic products and therefore cannot anticipate or render obvious the present claims.

The Examiner also rejected claims 24-34, 36-40 and 43 based on Chamat *et al.* The Chamat reference purports to disclose antibodies produced in mice against alprenolol, a synthetic beta adrenergic ligand, which were used to elicit anti-idiotypic responses in mice and rabbits (i.e., *in-vivo*). The Chamat reference does not teach or suggest using the antibodies (or the antiidiotypic antibodies) as a method of identifying compounds which have binding affinity for a target receptor. The antibodies generated by the Chamat reference bind to the ligand, alprenolol, but are not used for “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest”, (claims 24 and 45) or , “one or more compounds from synthetic products” (claims 44 or 46). Therefore, amended claim 24 and new claims 44-46 are neither anticipated nor obvious in view of the Chamat reference.

As claims 28-32, 34-43 depend from claim 24, these claims are also not anticipated or obvious in view of the Chamat reference.

Further, step (f) of new dependent claim 44 and new independent claim 46 both recite “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products” (emphasis added). Chamat does not teach or suggest the screening for one or more compounds from synthetic products and therefore cannot anticipate or render obvious the present claims.

The Examiner also rejected claims 24-27, 29-34, 36-40 and 43 based on Greene *et al.* The Greene reference purports to disclose that antiidiotype antibodies directed against neutralizing reovirus antibodies bind to the cell surface receptors specific for type 3 reovirus. The Greene reference further purports to identify peptides from the CDR of such antiidiotypic antibodies which, when used to generate an immune response in mice (i.e., *in-vivo*), result in antibodies which bind specifically to reovirus. The Greene reference concludes that there are corresponding sequences between the virus binding site on a cell and antiidiotype antibodies and “predicts the neutralizing epitope on the reovirus hemagglutinin.” (Col. 21, lines 15-62). The Greene reference, does not teach or suggest step (f) of amended independent claim 24 and new claims 44-46 which recite, “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds of interest”, (claims 24 and 45) or , “one or more compounds from synthetic products” (claims 44 or 46). Therefore, amended claim 24 and new claims 44-46 are neither anticipated nor obvious in view of the Greene reference. As claims 28-32, 34-43 depend from claim 24, these claims are also not anticipated or obvious in view of the Greene reference.

Further, step (f) of new dependent claim 44 and new independent claim 46 both recite “conducting a series of *in-vitro* assays utilizing said immobilized monoclonal antibodies to screen one or more compounds from synthetic products” (emphasis added). Greene does not

teach or suggest the screening for one or more compounds from synthetic products and therefore cannot anticipate or render obvious the present claims.

Applicants respectfully submit that the rejections under 35 U.S.C. §§ 102 and 103 of claim 24 have been overcome. As claims 28-32, 34-40 and 43 are dependent from claim 24 and incorporate all of its features, Applicants submit that these claims are also not anticipated or obvious in view of the cited references.

Applicants further submit that new dependent claim 44 and new independent claims 45 and 46 are not anticipated or obvious in view of any of the Examiner's cited references.

### **CONCLUSION**

In view of this response to the Examiner's restriction requirement, claim amendments and arguments presented, Applicants submit that the present application is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

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